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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03022040.4

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Anmelder/Applicant(s)/Demandeur(s):

ALTANA Pharma AG
Byk-Gulden-Strasse 2
78467 Konstanz
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Novel aminopyridine-derivatives

In Anspruch genommene Prioriät(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
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Novel Aminopyridine-Derivatives

Field of application of the invention

The invention relates to novel aminopyridine derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

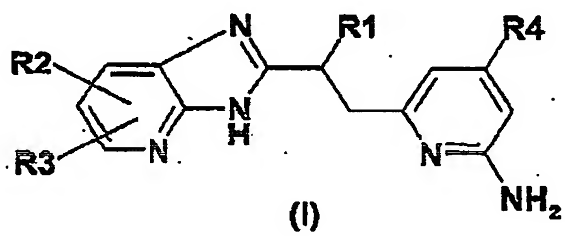
Known technical background

In the German Patent Application DE 2504252 and in the European Patent Application EP 0125756 3H-imidazo[4,5-b]pyridine derivatives with anti-ulcer activity are described.

Description of the invention

It has now been found that the aminopyridine derivatives, which are described in greater details below, have unanticipated, originative and sophisticated structural features and surprising and particularly advantageous properties.

The invention thus relates to compounds of formula I



(I)

in which

R1 is hydrogen or 1-4C-alkyl,

R2 is hydrogen, halogen, hydroxyl, nitro, amino, 1-7C-alkyl, trifluoromethyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono- or di-1-4C-alkylaminosulfonyl, 1-4C-alkylcarbonylamino, 1-4C-alkylsulfonylamino, phenyl, R21- and/or R211-substituted phenyl, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl wherein the phenyl moiety is substituted by R22, phenyl-1-4C-alkoxy, pyridyl, pyridyl substituted by R23, pyridyl-1-4C-alkyl, pyridyl-1-4C-alkyl wherein the pyridyl moiety is substituted by R24, in which

R21 is cyano, halogen, carboxyl, 1-4C-alkyl, 1-4C-alkoxy, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonyl, aminosulfonyl, mono- or di-

1-4C-alkylaminosulfonyl, amino, mono- or di-1-4C-alkylamino, trifluoromethyl, hydroxyl, phenylsulfonylamino or phenyl-1-4C-alkoxy,

R211 is halogen or 1-4C-alkoxy,

R22 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R23 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R24 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R4 is 1-4C-alkyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

1-4C-Alkyl is a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-7C-Alkyl is a straight-chain or branched alkyl radical having 1 to 7 carbon atoms. Examples are the heptyl, isoheptyl (5-methylhexyl), hexyl, isohexyl (4-methylpentyl), neohexyl (3,3-dimethylbutyl), pentyl, isopentyl (3-methylbutyl), neopentyl (2,2-dimethylpropyl), butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-4C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Alkoxy radicals having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

3-7C-Cycloalkyl stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. 3-7C-Cycloalkyl-1-2C-alkyl, particularly 3-7C-cycloalkylmethyl, radicals are to be emphasized in this connection. Examples which may be mentioned are the cyclopropylmethyl, the cyclohexylmethyl and the cyclohexylethyl radicals.

Halogen within the meaning of the present invention is iodine, bromine, chlorine or fluorine.

Completely or predominantly fluorine-substituted 1-4C-alkoxy is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy groups are replaced by fluorine atoms.

1-4C-Alkoxy-1-4C-alkoxy stands for one of the abovementioned 1-4C-alkoxy radicals which is substituted by the same or another of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the 2-(methoxy)ethoxy ($-O-CH_2-CH_2-O-CH_3$) and the 2-(ethoxy)ethoxy radical ($-O-CH_2-CH_2-O-CH_2-CH_3$).

1-4C-Alkoxy-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the 2-ethoxyethyl and the 3-methoxypropyl radical.

Mono- or Di-1-4C-alkylamino radicals contain in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Preferred are the di-1-4C-alkylamino radicals, especially the dimethylamino, the diethylamino and the diisopropylamino radicals.

Mono- or Di-1-4C-alkylaminocarbonyl radicals contain in addition to the carbonyl group one of the abovementioned mono- or di-1-4C-alkylamino radicals. Examples which may be mentioned are the N-methyl- the N,N-dimethyl-, the N-ethyl-, the N-propyl-, the N,N-diethyl- and the N-isopropylaminocarbonyl radical.

Mono-or Di-1-4C-alkylaminosulfonyl stands for a sulfonyl group to which one of the abovementioned mono- or di-1-4C-alkylamino radicals is bonded. Examples which may be mentioned are the methylaminosulfonyl, the dimethylaminosulfonyl and the ethylaminosulfonyl radical.

An 1-4C-Alkylcarbonylamino radical is, for example, the propionylamino [$C_3H_7C(O)NH-$] and the acetylamino radical [$CH_3C(O)NH-$].

An 1-4C-Alkylsulfonylamino radical is, for example, the propylsulfonylamino [$C_3H_7S(O)_2NH-$] and the methylsulfonylamino radical [$CH_3S(O)_2NH-$].

1-4C-Alkoxycarbonyl is a carbonyl group to which one of the abovementioned 1-4C-alkoxy radicals is bonded. Examples are the methoxycarbonyl [$CH_3O-C(O)-$] and the ethoxycarbonyl [$CH_3CH_2O-C(O)-$] radicals.

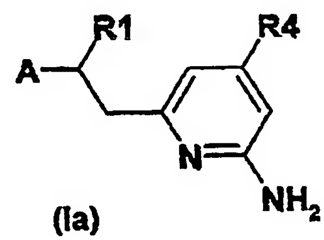
Phenyl-1-4C-alkoxy stands for one of the abovementioned 1-4C-alkoxy radicals, which is substituted by the phenyl radical. Examples which may be mentioned are the benzyloxy and the phenethoxy radical.

Phenyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by a phenyl radical. Examples which may be mentioned are the phenethyl and the benzyl radical.

Pyridyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by a pyridyl radical. Examples which may be mentioned are the pyridylethyl and the pyridylmethyl radical.

N-oxide denotes the N-oxide on the pyridine which is substituted by R4.

Compounds according to this invention which may be mentioned include for example compounds of formula Ia



(Ia)

in which R1 and R4 have the meanings given above and A suitably includes 3H-imidazo[4,5-b]pyridin-2-yl, 7-methyl-3H-imidazo[4,5-b]pyridin-2-yl, 5,7-dimethyl-3H-imidazo[4,5-b]pyridin-2-yl, 5-methoxy-3H-imidazo[4,5-b]pyridin-2-yl, 6-brom-3H-imidazo[4,5-b]pyridin-2-yl, 7-methoxy-3H-imidazo[4,5-b]pyridin-2-yl, 7-hydroxy-3H-imidazo[4,5-b]pyridin-2-yl, 7-ethoxy-3H-imidazo[4,5-b]pyridin-2-yl, 7-(2-methoxy-ethoxy)-imidazo[4,5-b]pyridin-2-yl, 7-(1,1,1-trifluoroethoxy)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(phenylethoxy)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(phenylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(tolylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(pyrid-4-ylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(pyrid-2-ylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(pyrid-3-ylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(4-methoxypyrid-2-ylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-phenyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-n-butyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-methylphenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-nitro-3H-imidazo[4,5-b]pyridin-2-yl, 6-(pyrid-3-yl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-cyanophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-methyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-trifluoromethyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-iodo-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-aminophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-dimethylaminophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-hydroxyphenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-trifluoromethylphenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-phenylsulfonylaminophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(3,4-dimethoxyphenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(3,4-dichlorophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(3,5-dichlorophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-benzyloxyphenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-benzyloxy-3-fluoro-phenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(3-methyl-butyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-cyclohexylmethyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-benzyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-ethyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-isopropyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-n-pentyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(2-fluorophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-bromophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(3-bromophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(3-methylphenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-phenethyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-(3-phenylpropyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-bromo-phenyl-methyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-acetamido-phenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-methoxycarbonyl-phenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-carboxy-phenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-methoxycarbonyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-dimethylamino-

carbonyl-phenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-dimethylaminosulphonyl-phenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-diethylaminosulphonyl-phenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-methylaminosulphonyl-phenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-aminosulphonyl-phenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-ethylaminosulphonyl-phenyl)-3H-imidazo[4,5-b]pyridin-2-yl or 6-(3-fluoro 4-dimethylaminosulphonyl-phenyl)-3H-imidazo[4,5-b]pyridin-2-yl.

Suitable salts for compounds of formula I - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-insoluble and, particularly, water-soluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are - depending on substitution - also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula I as well as all solvates and in particular all hydrates of the salts of the compounds of formula I.

A person skilled in the art knows on the base of his/her expert knowledge that the compounds according to this invention can exist, with regard to the fused imidazo ring, in different tautomeric forms such as e.g. in the 1-H form or, preferably, in the 3-H form, which is shown in formula I. The invention includes all conceivable tautomers in pure form as well as in any mixing ratio. Particularly the present invention includes the pure 1-H- and, preferably, 3-H-tautomers as well as any mixtures thereof.

Compounds according to this invention worthy to be mentioned are those compounds of formula I in which

R1 is hydrogen or 1-2C-alkyl,

R2 is hydrogen, halogen, phenyl, or R21-substituted phenyl, in which
R21 is 1-4C-alkyl, cyano, halogen, mono- or di-1-4C-alkylamino or trifluoromethyl,
R3 is hydrogen,
R4 is methyl,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds according to this invention more worthy to be mentioned are those compounds of formula I in which
R1 is hydrogen, methyl or ethyl,
R2 is hydrogen, iodine, bromine, phenyl, or R21-substituted phenyl, in which
R21 is methyl, cyano, chlorine, fluorine, dimethylamino or trifluoromethyl,
R3 is hydrogen,
R4 is methyl,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

The compounds of formula I according to the invention are, depending on the meanings of R1, chiral compounds. The invention includes all conceivable enantiomers in pure form as well as in any mixing ratio including the racemate.

A special embodiment of the compounds of the present invention include those compounds of formula I in which R4 is methyl.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R3 is hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is ethyl or, particularly, methyl.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is hydrogen and R4 is methyl.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R4 is methyl and R3 is hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R4 is methyl, R3 is hydrogen and R1 is ethyl, or in particular methyl, or in more particular hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which the substituent R2 is bonded to the 6-position of the imidazopyridine ring system.

The substituents R21 and R211 of compounds according to this invention can be attached in the ortho meta or para position with respect to the binding position in which the phenyl ring is bonded to the imidazopyridine ring system, whereby a special embodiment of the compounds of the present inventior include those compounds of formula I in which R211 is hydrogen and the substituent R21 is attached ii the para position.

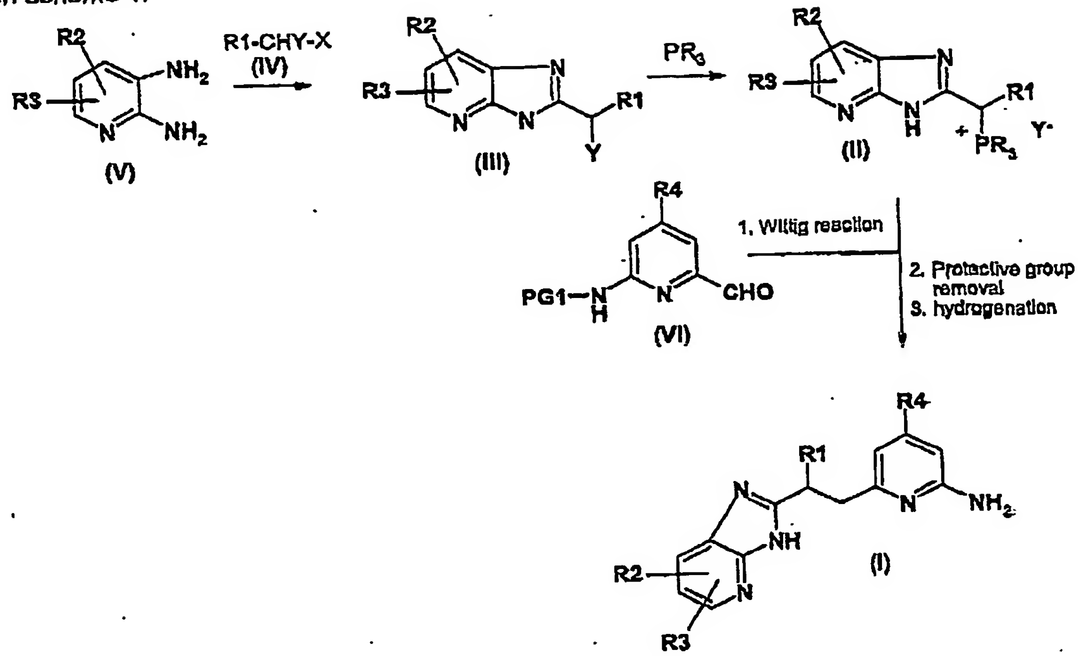
The compounds of formula I according to the invention can, for example, be prepared according to those synthesis routes specified and shown below or in a manner described by way of example in the following examples or analogously or similarly thereto.

Reaction scheme 1 below shows by way of example the preparation of compounds of formula I, in which R1, R2, R3 and R4 have the meanings indicated above. In a first reaction step, diamino compounds of formula V, in which R2 and R3 have the meanings indicated above, are converted into 3H-imidazo[4,5-b]pyridine derivatives in a manner known from the literature or with analogous or similar use of processes known from the literature. For example, said compounds of formula V can be reacted with carboxylic acids or carboxylic acid derivatives of formula IV, in which R1 has the meanings indicated above, Y is a suitable leaving group, advantageously chlorine, and X is a cyano or carboxyl radical, to give in a condensation reaction compounds of formula III, in which R1, R2, R3 and Y have the meanings mentioned above. This condensation reaction can be carried out as known to one of ordinary skill in the art or as described by way of example in the following examples, for example, by using a suitable condensing agent such as preferably polyphosphoric acid in a suitable inert solvent or, preferably, without further solvent using an excess of condensing agent, preferably at elevated temperature, in particular at 130°-170°C.

Alternatively, compounds of the formula III can be also obtained by art-known procedures according to literature (e.g. as described in L. Bukowski et al., Pharmazie 1999, 54(9), 651-654 or G. Cleve et al., Liebigs Ann. Chem. 1971, 747, 158-171).

Compounds of formula III, in which R1, R2, R3 and Y have the meanings mentioned above, can be converted with certain phosphanes into corresponding phosphonium salts. Preferably, compounds of formula III are reacted with tributylphosphane or triphenylphosphane to give corresponding compounds of formula II, in which R1, R2, R3 and Y have the meanings mentioned above and R is butyl or phenyl. Said reaction can be carried out in a manner habitual per se or as described in the following examples in a suitable solvent such as, for example, acetonitrile or N,N-dimethylformamide or a mixture thereof, at elevated temperature, preferably at 90°-150°C, optionally in the presence of an auxiliary such as tetrabutylammonium iodide.

Reaction scheme 1:



Compounds of formula II, in which R1, R2, R3 and Y have the meanings mentioned above and R is butyl or phenyl, are reacted with compounds of formula VI, in which R4 has the meanings given above and PG1 represents a suitable amino protective group, for example trityl or one of those mentioned in "Protective Groups in Organic Synthesis" by T. Greene and P. Wuts (John Wiley & Sons, Inc. 1999, 3rd Ed.) or in "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" by P. Kocienski (Thieme Medical Publishers, 2000). Said reaction can be carried out in a manner as described in the following examples or as known to the person skilled in the art according to a Wittig reaction. In the scope of this invention, said Wittig reaction is preferably carried out in a suitable solvent such as, for example, methanol, tetrahydrofurane, toluene or a mixture thereof, using a suitable base such as, for example, sodium hydride or sodium methanolate, at room temperature or at elevated temperature, preferably at 20°-80°C. With regard to the configuration of the exocyclic double bond obtained by Wittig reaction, the outcome can be a Z- or E-configurated product or, in particular, a mixture thereof.

In the step following the Wittig reaction, the compound(s) obtained are converted into the corresponding free amino compound(s) by removal of the abovementioned protective group PG1 in a manner customary per se. For example, when PG1 is trityl, detritylation can be obtained, for example, with the aid of aqueous acetic acid according to the procedure specified in the following examples.

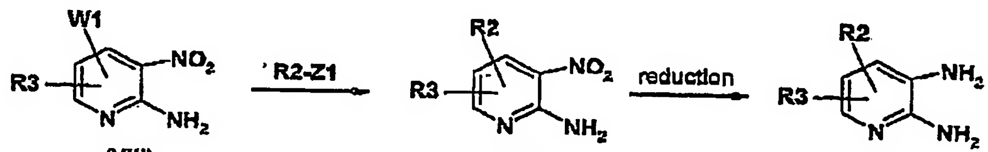
The reduction of the abovementioned exocyclic double bond following the deprotection reaction leads to desired compounds of formula I, in which R1, R2, R3 and R4 have the meanings given above. This reaction can be carried out as hydrogenation reaction according to procedures known to the person skilled in the art or according to the following examples in the presence of a suitable catalyst, such as, for example, palladium on active carbon or platinum dioxide, in a suitable solvent (e.g. in a lower

alcohol, such as, for example, methanol). If necessary, acid, such as trifluoracetic acid or acetic acid, can be added to the solvent.

Compounds of formula IV are commercially available or can be obtained in a known manner.

Compounds of formula V are also commercially available or are known e.g. from S.-X. Cai et al., J. Med. Chem. 1997, 40(22), 3679-3686 or from Cugola et al., Bioorg. Med. Chem. Lett. 1996, 22, 2749-2754 or can be prepared according to reaction scheme 2.

Reaction scheme 2:



(VIII) (VII) (V)

As shown in reaction scheme 2, in a first step compounds of formula VIII, in which R3 has the meanings mentioned above and W1 is a suitable leaving group (e.g. iodine or bromine), are reacted with boronic acids or boronic acid esters of formula R2-Z1, in which R2 is suitably phenyl or, in particular, R21- and/or R211-substituted phenyl and Z1 is a boronic acid group or a boronic acid ester group, under conditions appropriate for a Suzuki reaction to occur to give the corresponding compounds of formula VII.

Suitably, the Suzuki reaction is carried out as it is known to the person of ordinary skill in the art and/or in a manner as it is described below and specified by way of example in the following examples or analogously or similarly thereto.

The nitro group of compounds of formula VII is reduced in an art-known manner or as described in the following examples (e.g. with the aid of tin dichloride or by hydrogenation in the presence of a palladium catalyst) to give the corresponding diamino compounds of formula V.

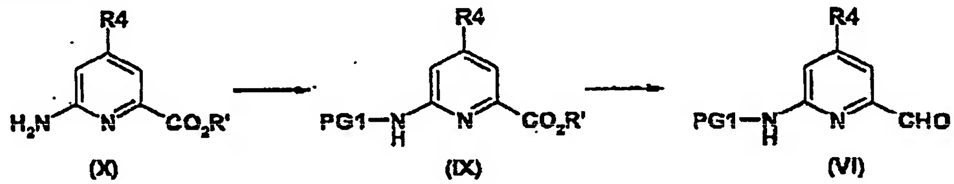
Compounds of formula VIII are known (e.g. commercially available) or can be prepared according to known procedures or analogously or similarly thereto.

Compounds of formula R2-Z1 are also known (e.g. commercially available) or can be obtained in an art-known manner or analogously or similarly thereto.

Compounds of formula VI, in which R4 has the meanings mentioned above and PG1 represents said suitable protective group, can be obtained, for example, as described in the following examples or as outlined in reaction scheme 3.

In a first step the amino group of ester compounds of formula X, in which R4 has the meanings indicated above and the moiety $-CO_2R'$ is preferably a methyl ester group, is protected by abovementioned suitable protective group PG1, preferably trityl, under standard conditions to afford corresponding compounds of formula IX.

Reaction scheme 3:

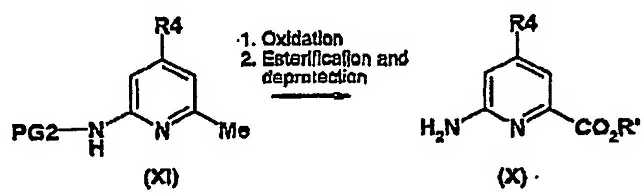


In a second step the ester group of compounds of formula IX, in which R4 has the meanings mentioned above and PG1 represents said suitable protective group, is reduced to give the desired compounds of formula VI. Said reduction reaction is carried out as described in the following examples or as known to the person skilled in the art using selective reducing agents such as, for example, suitable metal hydrids, particularly diisobutylaluminium hydride, in suitable solvents (e.g. toluene), optionally at reduced temperature..

Compounds of formula X, in which R4 has the meanings given above, are either known (see e.g. D. Markees et al. J. Am. Chem. Soc. 1956, 78, 4130-4133) or can be prepared as shown in the reaction scheme 4.

Reaction scheme 4 shows by way of example the synthesis of compounds of formula X, in which R4 is 1-4C-alkyl, particularly methyl, starting from corresponding compounds of formula XI, in which PG2 represents a suitable protective group, preferably acetyl. Thus in a first step, said compounds of formula XI are subjected to an oxidation reaction. This oxidation can be carried out in an art-known manner or as described in the following examples using a suitable oxidizing agent, such as, for example, potassium permangante. In a second step following oxidation the compounds obtained are converted into corresponding ester compounds – preferably the methyl ester compounds – of formula X. Said conversion can be carried out according to an art-known manner or as described in the following examples, e.g. using methanolic hydrochloric acid, preferably at boiling temperature, to obtain the methyl ester.

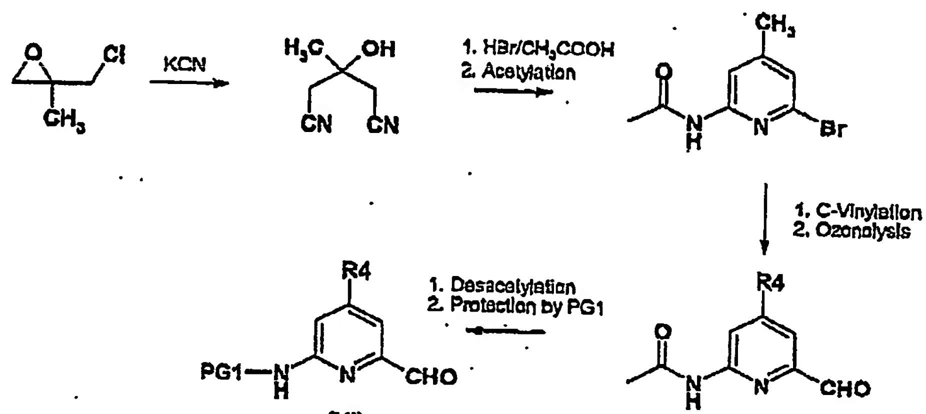
Reaction scheme 4:



Compounds of formula XI are known (e.g. from M. Belcher, J. Am. Soc. 1952, 74, 1916-1918) or can be prepared analogously or similarly to known procedures.

Altenatively, compounds of formula VI, in which R4 is methyl and PG1 has the meanings given above, can be also prepared according to the process outlined in reaction scheme 5.

Reaction scheme 5:



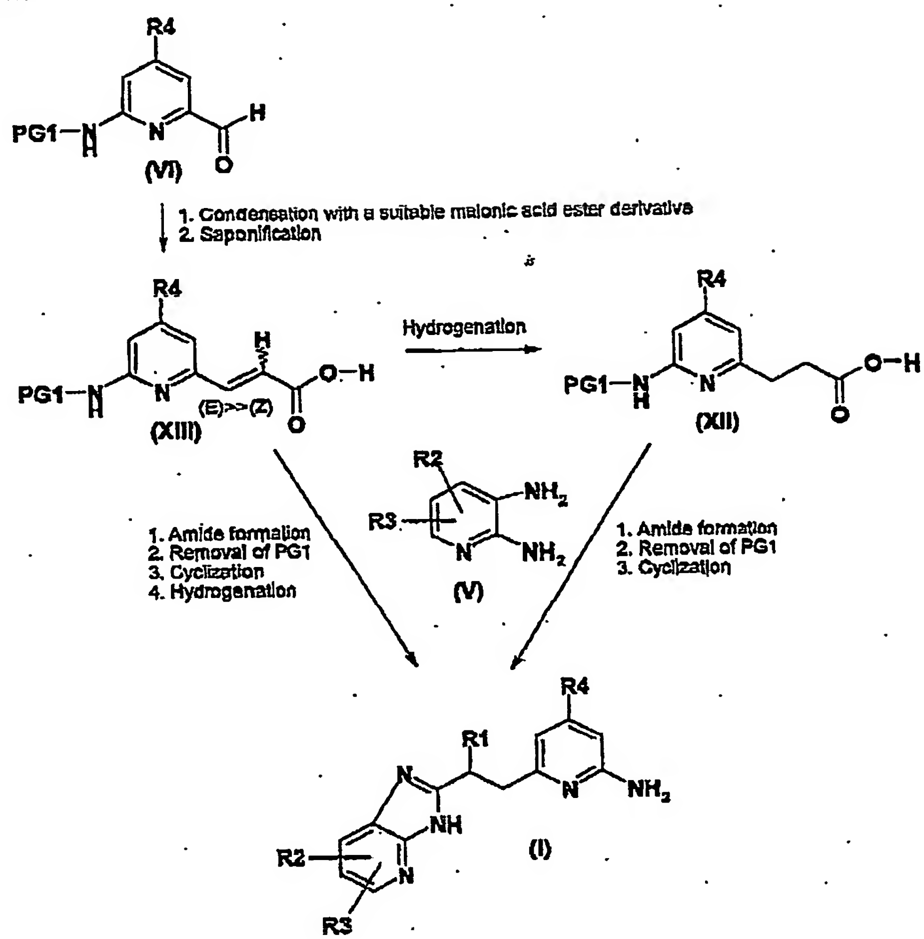
In an alternative, compounds of formula I, in which R1 is hydrogen and R2, R3 and R4 have the meanings given above, can be also obtained by the process shown in reaction scheme 6, described below and and specified by way of example in the following examples.

Thus, carbonic acid compounds of formula V, in which R1 and R2 have the meanings given above, are amidified with diamino compounds of formulae XII or XIII, in which R4 and PG1 have the meanings mentioned above, in a manner customary per se to the skilled person using suitable amide bond linking reagents (e.g. O-[(ethoxycarbonyl)canomethylene-amino]-N,N,N',N'-tetramethyluronium tetra-fluoroborate), the protective group PG1 is removed in an art-known manner and the amide is cyclized with the aid of an appropriate condensing agent (e.g. polyphosphoric acid) at elevated temperature. If the process started from compounds of formula XIII, the double bond is hydrogenated afterwards using standard procedures.

Accordingly, compounds of formula XII can be obtained from compounds of formula XIII by selective hydrogenation of the exocyclic double bond in a manner known to the skilled person (e.g. in the presence of palladium on carbon).

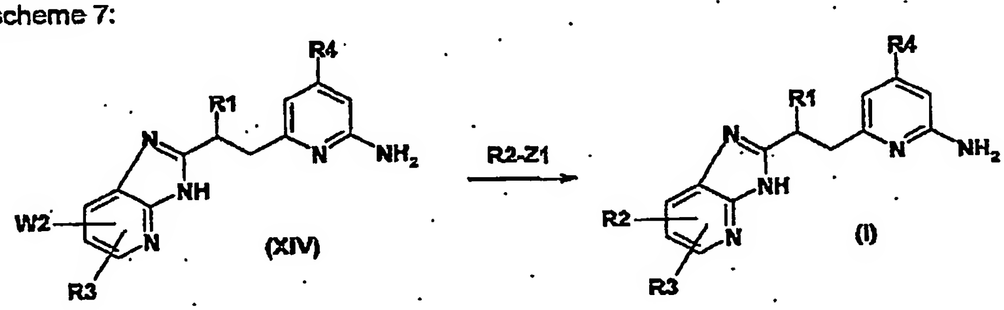
Compounds of formula XIII can be prepared starting from compounds of formula VI by lengthening of the exocyclic carbon chain, for example, by a Wittig reaction or, particularly, by a condensation reaction (with a malonic acid derivative, particularly with a malonic acid ester derivative) and subsequent saponification of the ester group. Said reactions can be carried out in a manner known to the skilled person or as described in the following examples or analogously or similarly thereto.

Reaction scheme 6:



In a further alternative, compounds of formula I, in which R1, R3, R4 have the meanings given above and R2 is phenyl or R21- and/or R211-substituted phenyl, can be also obtained as shown in reaction scheme 7 and specified by way of example in the following examples.

Reaction scheme 7:



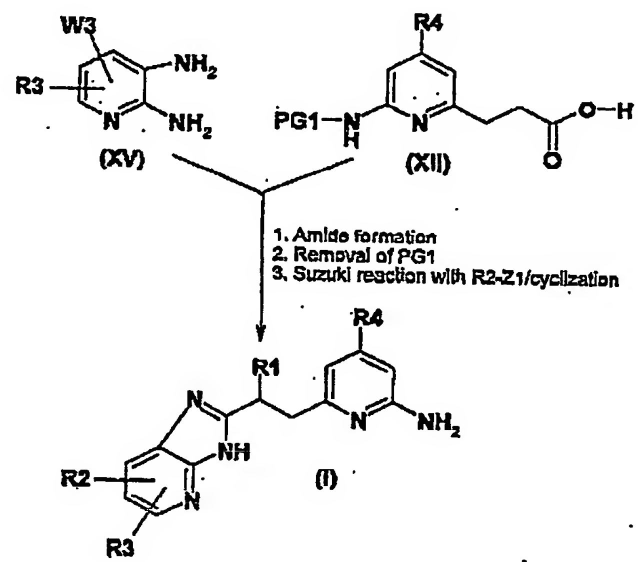
Compounds of formula XIV, in which R1, R3 and R4 have the meanings mentioned above and W2 is a suitable leaving group (e.g. iodine or bromine), are reacted with boronic acids or boronic acid esters of formula R2-Z1, in which R2 is suitably phenyl or, in particular, R21- and/or R211-substituted phenyl and

Z1 is a boronic acid group or a boronic acid ester group, under conditions appropriate for a Suzuki reaction to occur.

Compounds of formula XIV, in which R1, R3 and R4 have the meanings mentioned above and W2 is a suitable leaving group (e.g. iodine or bromine), can be prepared according to the synthesis routes disclosed in this invention or as described in the following examples or analogously or similarly thereto.

In still a further alternative, compounds of formula I, in which R1 is hydrogen, R3 and R4 have the meanings given above and R2 is phenyl or R21- and/or R211-substituted phenyl, can be also obtained as shown in reaction scheme 8 and specified by way of example in the following examples.

Reaction scheme 8:



As shown in reaction scheme 2, compounds of formula XV, in which R3 has the meanings given above and W3 is a suitable leaving group (e.g. iodine or bromine), can be converted with compounds of formula XII, in which R4 and PG1 has the meanings mentioned above, via amide bond formation reaction, removal of the protective group PG1 and, finally, Suzuki reaction with compounds of formula R2-Z1, in which R2 is phenyl or R21- and/or R211-substituted phenyl and Z1 has the meanings given above, into corresponding compounds of formula I, whereby under the conditions appropriate for the Suzuki reaction to occur simultaneously cyclization takes place.

Suitably, the Suzuki reactions according to this invention are carried out as it is known to the person of ordinary skill in the art and/or in a manner as it is described below and specified by way of example in the following examples or analogously or similarly thereto.

In more detail, the Suzuki reactions mentioned can be carried out in organic solvents alone, for example in toluene, benzene, dimethylformamide or in ethereal (e.g. dimethoxyethane or, in particular,

dioxane) or alcohol solvents or in a mixture thereof, or preferably in a mixture comprising an organic solvent (in particular dioxane) and water, with organic (e.g. triethylamine) or preferably inorganic base (e.g. potassium hydroxide, thallium hydroxide, sodium bicarbonate, cesium carbonate, cesium fluoride or potassium carbonate) in the presence of a transition metal catalyst, for example, a nickel or, in particular, palladium catalyst (e.g. $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$) or $PdCl_2(PCy_3)_2$, and, optionally, lithium chloride. The reaction is carried out at a temperature in the range from 20° to 160°C, usually 60° to 130°C for 10 minutes to 5 days, usually 30 minutes to 24 hours. Advantageously, the solvents used are degassed and the reaction is carried out under protective gas.

Boronic acids or boronic acid esters (e.g. pinacol esters) of formula R2-Z1, in which R2 and Z1 have the meanings given above, are known or can be obtained in an art-known manner or analogously or similarly to known compounds. Boronic acid esters (e.g. pinacol esters) of formula R2-Z1 can be prepared, for example, as described in the following examples starting from phenyl triflates or, particularly, phenyl halides, preferably the bromides or iodides, using e.g. bis-(pinacolato)-diboron in the presence of a transition metal, preferably palladium, catalyst. Optionally the boronic acid esters obtained can be isolated or, preferably, they are generated in situ and used in the subsequent Suzuki reaction without isolation.

Compounds of formula XV are known or can be prepared according to known procedures analogously or similarly to the preparation of known compounds.

The compounds of formula I can be converted, optionally, into their N-oxides, for example with the aid of hydrogen peroxide in methanol or with the aid of m-chloroperoxybenzoic acid in dichloromethane. The person skilled in the art is familiar on the basis of his/her expert knowledge with the reaction conditions which are specifically necessary for carrying out the N-oxidation.

It is known to the person skilled in the art that if there are a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in T. Greene and P. Wuts, "Protective Groups in Organic Synthesis" (John Wiley & Sons, Inc. 1999, 3rd Ed.) or in P. Kocienski, "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" (Thieme Medical Publishers, 2000).

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (for example a ketone like acetone, methylethylketone, or methylisobutylketone, an ether, like diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol, such as ethanol, isopropanol) which contains the desired acid, or to which the desired acid is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification into the free compounds which, in turn, can be converted into salts. In this manner, pharmacologically non-tolerable salts can be converted into pharmacologically tolerable salts.

Suitably, the conversions mentioned in this invention can be carried out analogously or similarly to methods which are familiar per se to the person skilled in the art, for example, in the manner which is described by way of example in the following examples.

The person skilled in the art knows on the basis of his/her knowledge and on the basis of those synthesis routes, which are shown and described within the description of this invention, how to find other possible synthesis routes for compounds according to this invention. All these other possible synthesis routes are also part of this invention.

Having described the invention in detail, the scope of the present invention is not limited only to those described characteristics or embodiments. As will be apparent to persons skilled in the art, modifications, analogies, variations, derivations, homologisations and adaptations to the described invention can be made on the base of art-known knowledge and/or, particularly, on the base of the disclosure (e.g. the explicite, implicite or inherent disclosure) of the present invention without departing from the spirit and scope of this invention.

The following examples illustrate the invention in greater detail, without restricting it. As well, further compounds according to the present invention, of which the preparation is explicitly not described, can be prepared in an analogous way or in a way which is known by a person skilled in the art using customary preparation methods and process techniques.

In the examples, m.p. stands for melting point, h for hours, d for days, min for minutes, TLC for thin layer chromatography, Rf for retention factor, MS for mass spectrum, M for molecular ion.

The compounds which are mentioned in the examples as well as their salts are preferred compounds of the invention.

Examples

Final products

1. 2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-3H-imidazo[4,5-b]pyridine

2.27 g of 4-methyl-2-(trityl-amino)-picolinaldehyde (compound A1) and 2.60 g of (3H-imidazo[4,5-b]pyridin-2-yl-methyl)-triphenyl-phosphonium chloride (compound A2) are suspended in a mixture of 41 ml of methanol, 9.1 ml of tetrahydrofurane and 4.5 ml of toluene. 4.60 ml of a solution of sodium methanolate in methanol (1.3 M) are added dropwise. The reaction mixture is stirred at 40°C for 3.5 h and evaporated to dryness. The resulting residue is chomatographed on silica gel using toluene/ethyl acetate 1:1 to give 3.93 g of a light yellow foam, which is suspended in 78 ml of 50% strength aqueous acetic acid and heated at 80°C for 0.5 h. The reaction mixture is filtered and the filtrate extracted twice with toluene. The combined organic phases are reextracted two times with water and the combined aqueous phases are evaporated to dryness to give 1.95 g of a yellow, amorpheous solid, which is dissolved as obtained in 250 ml of methanol. 2.40 ml of trifluoracetic acid and 430 mg of palladium on active carbon (10% Pd) are added and the suspension is stirred at room temperature for 3.5 d under hydrogen atmosphere. Then the catalyst is filtered off and the reaction mixture is conconcentrated to dryness. The residue is dissolved in dichloromethane and washed twice with a mixture of saturated sodium hydrogencarbonate solution/saturated sodium chloride solution (1:1). The organic phase is dried using sodium sulfate and concentrated to dryness. After chromatographical purification of the residue on silica gel (dichoromethane/methanol 8:1, 1% N,N-diisopropylethylamine), evaporation of the eluents and lyophillization from dioxane, 1.20 g of the title compound are obtained as a colorless lyophilisate. M.p. 45°-47°C. MS: 254.1 (MH^+). TLC: Rf = 0.40 (dichloromethane/methanol 8:1).

1a. 2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-3H-imidazo[4,5-b]pyridine hydrochloride

31 mg of 2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-3H-imidazo[4,5-b]pyridine (compound 1) are dissolved in 16 ml of dichloromethane. Under ice-cooling, 61 µl of a solution of hydrochloric acid in diethylether (2M strength) are added. The mixture is concentrated and the residue lyophillized from water to give 35 mg of the title compound as colorless lyophilisate. M.p. 136°C. MS: 254.2 (MH^+), 528.8 ($2MNa^+$).

1b. 2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-3H-imidazo[4,5-b]pyridine acetate

52 mg of 2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-3H-imidazo[4,5-b]pyridine (compound 1) are dissolved in 25 ml of dichloromethane. 2 ml of aqueous acetic acid (50% strength) are added. The mixture is concentrated and coevaporated successively with water and dichloromethane to give 65 mg of the title compound as foam. M.p. 54°C. MS: 254.2 (MH^+), 528.8 ($2MNa^+$).

2. (R,S)-2-[3-(2-Amino-4-methylpyridin-6-yl)prop-2-yl]-3H-imidazo[4,5-b]pyridine

Starting from 4-methyl-2-(trityl-amino)-picolinaldehyde (compound A1) and {1-(3H-imidazo[4,5-b]pyridin-2-yl)-ethyl}-triphenyl-phosphonium chloride (compound A3) the title compound is obtained analogously to the procedure as in example 1. M.p. 48°C. MS: 268.1 (MH^+).
TLC: Rf = 0.20 (dichloromethane/methanol 10:1).

3. (R,S)-2-[4-(2-Amino-4-methylpyridin-6-yl)but-2-yl]-3H-imidazo[4,5-b]pyridine

A solution of 0.632 g of tributyl-{1-(3H-imidazo[4,5-b]pyridin-2-yl)-propyl}-phosphonium chloride (compound A4) in tetrahydrofurane is added to a suspension of 63 mg of sodium hydride (60% strength suspension in paraffin) in 3.75 ml of tetrahydrofurane. After 15 min stirring, a solution of 0.500 g of 4-methyl-2-(trityl-amino)-picolinaldehyde (compound A1) in tetrahydrofurane is added dropwise and the reaction mixture is heated at 80°C for 6 h. The mixture is then evaporated to dryness and the resulting residue chomatographed on silica gel using toluene/ethyl acetate 5:1 to give 0.266 g of a light yellow oil, which is suspended in 6 ml of 50% strength aqueous acetic acid and heated at 80°C for 0.5 h. The reaction mixture is filtered and the filtrate extracted twice with toluene. The combined organic phases are reextracted two times with water and the combined aqueous phases are evaporated to dryness to give 0.146 g of a yellow, waxen solid, which is dissolved as obtained in 19 ml of methanol. 0.21 ml of trifluoracetic acid and 32 mg of palladium on active carbon (10% Pd) are added and the suspension is stirred at room temperature for 2.5 d under hydrogen atmosphere. Then the catalyst is filtered off and the reaction mixture is conconcentrated to dryness. The residue is dissolved in dichloromethane and washed twice with a mixture of saturated sodium hydrogencarbonate solution/ saturated sodium chloride solution (1:1). The organic phase is dried using sodium sulfate and concentrated to dryness. After chromatographical purification of the residue on silica gel (dichoromethane/methanol 8:1), evaporation of the eluents and lyophillization from dioxane, 0.170 g of the title compound are obtained as a hygroscopic lyophilisate. M.p. 164°-166°C. MS: 282.1 (MH^+).
TLC: Rf = 0.24 (dichloromethane/methanol 10:1).

4. 2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-6-bromo-3H-imidazo[4.5-b]pyridine

A solution of 1.22 g of (6-bromo-3H-imidazo[4,5-b]pyridin-2-yl-methyl)-tributyl-phosphonium chloride (compound A5) in tetrahydrofurane is added to a suspension of 109 mg of sodium hydride (60% strength suspension in paraffin) in 15.3 ml of tetrahydrofurane. After 15 min stirring, a solution of 0.856 g of 4-methyl-2-(trityl-amino)-picolinaldehyde (compound A1) in tetrahydrofurane is added dropwise and the reaction mixture is heated at 80°C for 6 h. The mixture is then evaporated to dryness and the resulting residue chomatographed on silica gel using toluene/ethyl acetate 5:1 to give 0.672 g of a yellow solid, which is suspended in 14 ml of 50% strength aqueous acetic acid and heated at 80°C for 1.5 h. The reaction mixture is filtered and the filtrate extracted twice with toluene. The combined organic phases are reextracted two times with water and the combined aqueous phases are evaporated to

dryness to give 0.355 g of a yellow, amorpheous solid. 0.300 g of said solid are dissolved in 112 ml of methanol. 0.14 ml of glacial acetic acid and 14 mg of platinum dioxide are added and the suspension is stirred at room temperature for 2.5 d under hydrogen atmosphere. Then the catalyst is filtered off and the reaction mixture is conconcentrated to dryness. The residue is dissolved in dichloromethane and washed twice with a mixture of saturated sodium hydrogencarbonate solution/saturated sodium chloride solution (1:1). The organic phase is dried using sodium sulfate and concentrated to dryness. After chromatographical purification of the residue on silica gel (dichoromethane/methanol 20:1) and evaporation of the eluents, 0.118 g of the title compound are obtained as an amorpheous solid. M.p. 190°-194°C. TLC: Rf = 0.50 (dichloromethane/methanol 8:1).

5. <u>2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-6-phenyl-3H-imidazo[4,5-b]pyridine</u>

350 mg of 2-[2-(amino-4-methylpyridin-6-yl)ethyl]-6-bromo-3H-imidazo[4,5-b]pyridine (compound 4) are dissolved in 5.6 ml of anoxic dioxane under a nitrogen atmosphere. Subsequently, 3.15 ml of an aqueous sodium bicarbonate solution (2.0 M), 193 mg of 2-phenyl-1,3,2-dioxaborinane, and 49 mg of *trans*-dichloro-bis(tricyclohexylphosphane)palladium-(II) are added. The reaction mixture is refluxed at 110°C for 46 hours. Thereafter, the volatile components are removed in vacuo and the remaining residue is redissolved in 200 ml of a mixture of water/dichloromethane (1:1). The aqueous phase is extracted twice each with 125 ml of dichloromethane. The organic layer is separated, dried using sodium sulfate, and evaporated to dryness to yield a colorless, crude solid. Subsequently, the residue is purified by flash chromatography on silica gel (eluent: dichloromethane/methanol 8:1) to afford 279 mg of the title compound as a colorless solid of m.p. 230°C. MS: 330.3 (MH^+). TLC: Rf = 0.34 (dichloromethane/methanol 8:1).

6. <u>2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-6-(4-cyano-phenyl)-3H-imidazo[4,5-b]pyridine</u>

296 mg of 2-[2-(amino-4-methylpyridin-6-yl)ethyl]-6-bromo-3H-imidazo[4,5-b]pyridine (compound 4) are dissolved in 4.74 ml of anoxic dioxane under a nitrogen atmosphere. Subsequently, 2.7 ml of an aqueous sodium bicarbonate solution (2.0 M), 231 mg of benzonitrile-4-boronic acid pinacolester, and 42 mg of *trans*-dichloro-bis(tricyclohexylphosphane)palladium-(II) are added. The reaction mixture is refluxed at 110°C for 70 hours. Thereafter, the volatile components are removed in vacuo and the remaining residue is redissolved in 150 ml of a mixture of water/dichloromethane (1:1). The aqueous phase is extracted twice each with 100 ml of dichloromethane. The organic layer is separated, dried using sodium sulfate, and evaporated to dryness to yield a colorless, crude solid. Subsequently, the residue is purified by flash chromatography on silica gel (eluent: dichloromethane/methanol 8:1) to afford 127 mg of the title compound as a colorless solid of m.p. 218°C. MS: 355.3 (MH^+). TLC: Rf = 0.35 (dichloromethane/methanol 8:1).

7. **2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-6-p-tolyl-3H-imidazo[4,5-b]pyridine**

To a solution of 340 mg of (*E,Z*)-2-[2-(2-amino-4-methylpyridin-6-yl)vinyl]-6-p-tolyl-3H-imidazo[4,5-b]pyridine (compound A6) in 28 ml of methanol is added 0.308 ml of trifluoroacetic acid and 153 mg of palladium on active carbon (10% Pd). The suspension is vigorously stirred at 50°C for 4.5 d under a hydrogen atmosphere. Then the catalyst is filtered off and the reaction mixture is conconcentrated to dryness. The residue is dissolved in dichloromethane and washed twice with a mixture of saturated sodium hydrogencarbonate solution/saturated sodium chloride solution (1:1). The organic phase is dried using sodium sulfate and concentrated to dryness. After chromatographical purification of the residue on silica gel (dichoromethane/methanol 8:1) and evaporation of the eluents 52 mg of the title compound are obtained as an oil. MS: 344.4 (MH^+). TLC: Rf = 0.37 (dichloromethane/methanol 8:1).

7a. **2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-6-p-tolyl-3H-imidazo[4,5-b]pyridine hydrochloride**

41 mg of 2-[2-(2-amino-4-methylpyridin-6-yl)ethyl]-6-p-tolyl-3H-imidazo[4,5-b]pyridine (compound 7) are dissolved in 8.4 ml of dichloromethane. After cooling the solution to 0°C, 61 µl of hydrochloride in diethyl ether (strength 2.0 M) is added under stirring. Subsequently, the solvents are evaporated in vacuo. The remaining residue is redissolved in petrol ether/dichloromethane (3:1) and concentrated to dryness to afford 40 mg of the title compound as an amorphous pulver of m.p. 186°C. MS: 344.4 (MH^+). TLC: Rf = 0.37 (dichloromethane/methanol 8:1).

Starting from the appropriate starting compounds, which are described below or which can be prepared analogously or similarly to the described compounds in a manner known to the person skilled in the art, the following Examples 8 to 9 are obtained according to the procedure as in Examples 7 or 7a and the following Examples 10 to 12 are obtained in such a way as disclosed in the description of this invention.

8. **2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-6-(4-fluoro-phenyl)-3H-imidazo[4,5-b]pyridine**

9. **2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-6-(4-dimethylamino-phenyl)-3H-imidazo[4,5-b]pyridine**

9a. **2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-6-(4-dimethylamino-phenyl)-3H-imidazo[4,5-b]pyridine hydrochloride**

10. **2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-6-(4-chloro-phenyl)-3H-imidazo[4,5-b]pyridine**

Compound 10 can be prepared by a person skilled in the art according to reaction scheme 6 specified above in an art-known manner applying customary preparation methods and similarly to the Examples

described explicitly herein starting with reaction of a compound of formula XII, in which PG1 is trityl and R4 is methyl, with compound F4.

11. 2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-6-(4-iodo-phenyl)-3H-imidazo[4,5-b]pyridine

Compound 11 can be prepared by a person skilled in the art according to reaction scheme 6 specified above in an art-known manner applying customary preparation methods and similarly to the Examples described explicitly herein starting with reaction of a compound of formula XII, in which PG1 is trityl and R4 is methyl, with art-known compound 2,3-diamino-5-iodo-pyridine.

12. 2-[2-(2-Amino-4-methylpyridin-6-yl)ethyl]-6-(4-trifluoromethyl-phenyl)-3H-imidazo[4,5-b]pyridine

Compound 12 can be prepared by a person skilled in the art according to reaction scheme 8 specified above in an art-known manner applying customary preparation methods and similarly to the Examples described explicitly herein starting with reaction of a compound of formula XII, in which PG1 is trityl and R4 is methyl, with art-known compound 2,3-diamino-5-iodo-pyridine.

Starting materials

A1. 4-Methyl-2-(trityl-amino)-picolinaldehyde

A solution of 1.0 g of 4-methyl-2-(trityl-amino)-picolinic acid methyl ester (compound B1) in 35 ml of toluene is treated dropwise at –70°C with 2.9 ml of a 1.5 M solution of diisobutylaluminium hydride in toluene. After 0.5 h 5 ml of diethylether and 2.9 ml of diluted aqueous acetic acid (20% strength) are added. After further 0.5 h the reaction mixture is warmed to room temperature and 29 ml of an aqueous solution of ammonia (25% strength) are added. The colorless precipitate is filtered off with suction and washed with toluene. The filtrate is extracted with brine, the organic phase is dried using sodium sulfate and concentrated to dryness. After purification of the crude product on silica gel (eluent: toluene/ethyl acetate 20:1) and evaporation of the eluents, 0.438 g of the title compound are obtained as a colorless, amorpheous solid. M.p. 213°C. MS: 379.1 (MH^+). TLC: Rf = 0.66 (toluene/acetone 10:1).

A2. (3H-Imidazo[4,5-b]pyridin-2-yl-methyl)-triphenyl-phosphonium chloride

3.18 g of chloromethyl-3H-imidazo[4,5-b]pyridine (G. Cleve et al., Liebigs Ann. Chem. 1971, 747, 158-171) are suspended in 16 ml of N,N-dimethylformamide and 50 ml of acetonitrile. 4.98 g of triphenylphosphine are added and the mixture is heated to 100°C for 3 h. The mixture is concentrated to dryness and the crude product purified by chromatography on silica gel (eluent: dichloromethane/methanol 10:1 to 8:1) to afford 3.15 g of the title compound as a beige, amorpheous solid. M.p. 302°C. MS: 394.3 (M^+).

A3. {1-(3H-Imidazo[4,5-b]pyridin-2-yl)-ethyl}-triphenyl-phosphonium chloride

8.66 g of 2-(1-chloroethyl)-3H-imidazo[4,5-b]pyridine (compound B2) are suspended in 40 ml of N,N-dimethylformamide and 120 ml of acetonitrile. 12.6 g of triphenylphosphine are added and the mixture is heated to 150°C for 17 h. The mixture is concentrated to dryness and the crude product purified by chromatography on silica gel (eluent: dichloromethane/methanol 20:1) to afford 4.16 g of the title compound as an oil. MS: 408.0 (M^+).

A4. Tributyl-{1-(3H-imidazo[4,5-b]pyridin-2-yl)-propyl}-phosphonium chloride

8.66 g of 2-(1-chloropropyl)-3H-imidazo[4,5-b]pyridine (compound B3) are suspended in 18 ml of N,N-dimethylformamide and 61 ml of acetonitrile. 6.3 ml of triphenylphosphine are added at 40°C and the mixture is heated to 90°C for 16 h. The mixture is concentrated to dryness to give 11.9 g of the title compound as an oil. MS: 362.2 (M^+).

A5. (6-Bromo-3H-imidazo[4,5-b]pyridin-2-yl-methyl)-tributyl-phosphonium chloride

4.0 g of 6-bromo-2-chloromethyl-3H-imidazo[4,5-b]pyridine (compound B4) are suspended in 16 ml of N,N-dimethylformamide and 54 ml of acetonitrile. 4.9 ml of triphenylphosphine and 0.599 g of tetrabutylammonium iodide are added sequentially at 40°C and the mixture is heated to 90°C for 20 h. The mixture is concentrated to dryness to give the 8.94 g of the crude title compound as an oil. MS: 412.3, 414.2 (M^+).

A6. (*E,Z*)-2-[2-(2-Amino-4-methylpyridin-6-yl)vinyl]-6-p-tolyl-3H-imidazo[4,5-b]pyridine

436 mg of (*E,Z*)-3-N-[(2-amino-4-methylpyridin-6-yl)-propen-1-on-3-yl)-2,3-diamino-5-p-tolyl-pyridine amide (compound B5) are treated with 17 g polyphosphoric acid at 125°C for 24 h. Thereafter, 190 ml of water are carefully added at 100°C under continuous stirring. Subsequently, the solution is cooled to room temperature and treated with 35 ml of an aqueous sodium hydroxide solution (strength 9.0 M) adjusting pH = 7. The neutral solution is extracted four times each with 100 ml of ethyl acetate. The combined organic phases are reextracted twice each using 80 ml of brine, subsequently dried using sodium sulfate, filtered with suction, and concentrated in vacuo to obtain 340 mg of the title compounds as an amorphous solid. MS: 342.4 (MH^+). TLC: Rf = 0.53 (dichloromethane/methanol 8:1).

B1. 4-Methyl-2-(trityl-amino)-picolinic acid methyl ester

A solution of 40.0 g of 2-acetylamino-4,6-dimethyl-pyridine (M. Belcher, J. Am. Chem. Soc. 1952, 74, 1916-1918) in a mixture of 127 ml of tert-butanol and 375 ml of water is treated portionwise (max 3.0 g each) at 75°C with 92 g of potassium permanganate. After completion of the addition, the reaction mixture is heated at 80°C for 3 h. Afterwards, the reaction mixture is filtered over cellite and the filter cake is rinsed with water. Under cooling unreacted 2-acetylamino-4,6-dimethyl-pyridine precipitates

from the filtrate and is filtered off with suction. The mother liquor is concentrated to ¼ of its volume and adjusted to pH 5 with the aid of concentrated hydrochloric acid. The precipitate is filtered off, dried, dissolved in 300 ml of methanolic hydrochloric acid (2.2 M strength) and heated at 80°C for 15 h. After evaporation to dryness, the residue is dissolved in 200 ml of water, 100 ml of dichloromethane are added and the mixture is neutralized by addition of sodium hydrogencarbonate. The phases are separated and the water phase is reextracted two times each with 200 ml of dichloromethane. The combined organic phases are dried using sodium sulfate and concentrated to dryness to give 12.1 g of crude 2-amino-4-methyl-picolinic acid methyl ester, which is dissolved in 180 ml of dichloromethane and treated with 22.2 g of trityl chloride and 15 ml of N,N-diisopropylethylamine. After 16 h the reaction mixture is extracted with a mixture of saturated sodium hydrogencarbonate solution/saturated sodium chloride solution (1:1), the organic phase is dried over sodium sulfate and the solvents are evaporated. The crude product is purified by chromatography on silica gel to give 18.5 g of the title compound as a colorless oil. MS: 409.1 (MH^+). TLC: Rf = 0.37 (toluene/acetone 10:1).

B2. <u>2-(1-Chloroethyl)-3H-imidazo[4,5-b]pyridine</u>

5.2 g of 2,3-diaminopyridine in 209 g of polyphosphoric acid are heated at 120°C for 0.5 h. The solution is cooled to 80°C and 4.6 ml of 2-chloropropionitrile are added. Thereafter, the reaction mixture is heated to 180°C for 2.5 h. After cooling, the polyphosphoric acid is hydrolysed with water, the mixture is filtered using charcoal and celite and the pH value of the filtrate is adjusted to pH 4 using 9 M aqueous sodium hydroxide solution. The mixture is extracted twice each with 250 ml of ethyl acetate, the combined organic phases are dried using sodium sulfate, concentrated and lyophilised from ethanol/water to give 3.56 g of the title compound as a light brown, amorpheous solid. M.p. 132°C. TLC: Rf = 0.60 (dichloromethane/methanol 8:1).

B3. <u>2-(1-Chloropropyl)-3H-imidazo[4,5-b]pyridine</u>

5.0 g of 2,3-diaminopyridine in 200 g of polyphosphoric acid are heated at 120°C for 0.5 h. The solution is cooled to 80°C and 5.7 ml of 2-chlorobutyric acid are added. Thereafter, the reaction mixture is heated to 130°C for 22 h. After cooling, the polyphosphoric acid is hydrolysed with water, the mixture is filtered using charcoal and celite and the pH value of the filtrate is adjusted to pH 4 using 9 M aqueous sodium hydroxide solution. The mixture is extracted three times each with 200 ml of ethyl acetate, the combined organic phases are dried using sodium sulfate, concentrated and purified by chromatography on silica gel (eluent: toluene/ethyl acetate 1:1) to give 5.19 g of the title compound as a colorless, amorpheous solid. M.p. 137°C. TLC: Rf = 0.50 (dichloromethane/methanol 10:1).

B4. <u>6-Bromo-2-chloromethyl-3H-imidazo[4,5-b]pyridine</u>

3.0 g of 5-bromo-2,3-diaminopyridine (S.-X. Cai et al., J. Med. Chem. 1997, 40(22), 3679-3686) in 120 g of polyphosphoric acid are heated at 160°C for 0.5 h. The solution is cooled to 100°C and 1.26 ml of

chloroacetonitrile are added. Thereafter, the reaction mixture is heated to 170° C for 22 h. After cooling the polyphosphoric acid is hydrolysed with water, the mixture is filtered using charcoal and celite and the pH value of the filtrate is adjusted to pH 4 using 9 M aqueous sodium hydroxide solution. The precipitate is collected, suspended in 100 ml of hot methanol and filtered over celite. The filtrate is concentrated to dryness to afford 2.78 g of the title compound as a beige, amorpheous solid. TLC: Rf = 0.42 (dichloromethane/methanol 10:1).

B5. __(*E,Z*)-3-N-[(2-Amino-4-methylpyridin-6-yl)-propen-1-on-3-yl)-2,3-diamino-5-p-tolyl-pyridine amide__

1.30 g of (*E,Z*)-3-N-{[4-methyl-(2-trityl-amino)-pyridin-6-yl]-propen-1-on-3-yl}-2,3-diamino-5-p-tolyl-pyridine amide (compound C1) are dissolved in 75 ml of aqueous acetic acid (50% strength) and heated at 80°C for 2 h. Subsequently, the resulting colorless precipitate is filtered off and rinsed with water. The filtrate is concentrated to dryness and coevaporated twice each with 20 ml of toluene. The residue is purified by chromatography on silica gel (eluent: dichloromethane/methanol 10:1) to yield 436 mg of the title compounds after evaporation of eluents as a colorless oil. MS: 360.2 (MH^+), 718.9 ($2MH^+$). TLC: Rf = 0.15 (dichloromethane/methanol 10:1).

C1. __(*E,Z*)-3-N-{[4-Methyl-(2-trityl-amino)-pyridin-6-yl]-propen-1-on-3-yl}-2,3-diamino-5-p-tolyl-pyridine amide__

1.2 g of (*E,Z*)-4-methyl-2-(trityl-amino)-pyridine-6-(propen-3-ylic) acid (compound D1) and 568 mg of 2,3-diamino-5-p-tolyl-pyridine (compound F1) are dissolved in 53 ml of pyridine and sequentially treated with 1.12 g of O-[(ethoxycarbonyl)canomethylene-amino]-N,N,N',N'-tetramethyluronium tetrafluoroborate and 0.611 ml of diisopropylethyl amine. The reaction mixture is warmed to 65°C for 24 h. After completion of the amide formation (TLC), the solution is concentrated in vacuo and coevaporated three times each with 20 ml of toluene. The crude product is purified by chromatography on silica gel (eluent: dichloromethane/methanol 15:1) to afford 1.3 g of the title compounds as colorless oil. MS: 602.3 (MH^+). TLC: Rf = 0.45-0.47 (dichloromethane/methanol 10:1).

D1. __(*E,Z*)-[4-Methyl-2-(trityl-amino)-pyridin-6-yl]-propen-3-ylic acid__

1.62 g of (*E,Z*)-[4-methyl-2-(trityl-amino)-pyridin-6-yl-]-propen-3-ylic acid methyl ester (compound E1) are dissolved in 70 ml of tetrahydrofurane. Subsequently, 37.3 ml of a 1.0 M solution of aqueous sodium hydroxide are added and the reaction mixture is warmed to 50°C for 27 h. At room temperature 22 g of amberlite IR-120 [H^+] are added und the suspension is stirred for 15 min neutralizing the reaction mixture. The ion exchange resin is removed by filtration and 1.19 g of the title compounds are isolated as a colorless solid after evaporation of solvent of m.p. 147°C. MS: 421.0 (MH^+). TLC: Rf = 0.45 (dichloromethane/methanol 10:1).

E1. (E,Z)-[4-methyl-2-(trityl-amino)-pyridin-6-yl-]-propen-3-ylic acid methyl ester

Under ice-cooling, a suspension of 190 mg of sodium hydride (60% strength suspension in paraffin) in 15 ml of tetrahydrofurane is treated with a solution of 1.78 g of methyl diethyl phosphonoacetate in 7.6 ml of tetrahydrofurane. After stirring at 0°C for 30 min, a suspension of 2.3 g of 4-methyl-2-(trityl-amino)-picolinaldehyde (compound A1) in 15 ml of tetrahydrofurane is added. The reaction mixture is stirred for 70 h at room temperature. Thereafter, the mixture is treated with 20 ml of a saturated aqueous ammonium chloride solution for 30 min. The solution is diluted with 30 ml of water and extracted three times each with 50 ml of diethyl ether. The organic layer is separated, dried using sodium sulfate, filtered with suction, and concentrated in vacuo to yield a crude oil of the title compound. After chromatographical purification of the residue on silica gel (toluene/ethyl acetate 20:1) and evaporation of the eluents, 6.6 g of the title compounds are obtained as a colorless oil. MS: 435,0 (MH^+). TLC: Rf = 0.45 (toluene/ethyl acetate 20:1).

F1. 2,3-Diamino-5-p-tolyl-pyridine

A solution of 3.25 g of 2-amino-5-(p-tolyl)-3-nitro-pyridine (compound G3) and 325 mg of Pd/C (10%) in 260 ml of methanol is treated with hydrogen under vigorous stirring at room temperature for 18 h. The suspension is filtered with suction through a celite pad. The colorless filtrate is evaporated to dryness to afford 2.63 g of the pure title compound of m.p. 141°C. MS: 200.3 (MH^+).
TLC: Rf = 0.46 (dichloromethane/methanol 10:1).

F2. 2,3-Diamino-5-(4-fluoro-phenyl)-pyridine

A solution of 2.59 g of 2-amino-5-(4-fluorophenyl)-3-nitro-pyridine (compound G1) in 36 ml ethanol is treated with 12.9 g of $SnCl_2 \cdot 2H_2O$ at 90°C for 24 h under a nitrogen atmosphere. Thereafter, the solution is concentrated to dryness. The residue is dissolved in 600 ml H_2O and adjusted to pH 8 using a 1.0 M solution of aqueous sodium hydroxide. Subsequently, the aqueous layer is extracted six times each with 50 ml of ethyl acetate. The combined organic phases are extracted once with 100 ml of brine, dried using magnesium sulfate, filtered with suction, and evaporated to dryness to yield 2.12 g of the pure title compound of m.p. 261°C. MS: 204.3 (MH^+). TLC: Rf = 0.50 (dichloromethane/methanol 5:1).

F3. 2,3-Diamino-5-(4-dimethylamino-phenyl)-pyridine

A solution of 3.30 g of 2-amino-5-(4-dimethylaminophenyl)-3-nitro-pyridine (compound G2) and 330 mg of Pd/C (10%) in 260 ml of methanol is treated with hydrogen under vigorous stirring at room temperature for 17 h. The suspension is filtered with suction through a celite pad. The colorless filtrate is evaporated to dryness to afford 2.85 g of the pure title compound of m.p. 155°C. MS: 229.3 (MH^+).
TLC: Rf = 0.38 (dichloromethane/methanol 10:1).

F4. 2,3-Diamino-5-(4-chlorophenyl)-pyridine

A solution of 1.19 g of 2-amino-5-(4-chlorophenyl)-3-nitro-pyridine in 17 ml of ethanol is treated with 5.5 g of $SnCl_2 \cdot 2H_2O$ at 90°C for 17 h under a nitrogen atmosphere. Thereafter, the solution is concentrated in vacuo to dryness. The residue is dissolved in 300 ml of water and adjusted to pH 8 using a 1.0 M solution of aqueous sodium hydroxide. Subsequently, the aqueous layer is extracted four times each with 50 ml of ethyl acetate. The combined organic phases are extracted once with 50 ml of brine, dried using $MgSO_4$, filtered with suction, and evaporated to dryness to yield 1.05 g of the pure title compound of m.p. 178°C. MS: 220.3 (MH^+). TLC: Rf = 0.30 (dichloromethane/methanol 5:1).

G1. 2-Amino-5-(4-fluoro-phenyl)-3-nitro-pyridine

5.0 g of 2-amino-5-bromo-3-nitropyridine are dissolved in 120 ml of anoxic dioxane under a nitrogen atmosphere. Subsequently, 69 ml of an aqueous sodium bicarbonate solution (2.0 M), 5.4 g of 4-fluorophenyl-boronic acid, and 1.0 g of *trans*-dichloro-bis(tricyclohexylphosphane)palladium-(II) are added. The reaction mixture is refluxed at 110°C for 17 hours. Thereafter, the volatile components are removed in vacuo and the remaining residue is redissolved in 2.0 l of a mixture of water/dichloromethane (1:1). The aqueous phase is extracted four times each with 625 ml of dichloromethane. The organic layer is separated, dried using sodium sulfate, and evaporated to dryness to yield a colorless, crude solid. Subsequently, the residue is purified by flash chromatography on silica gel (eluent: toluene/ethyl acetate 20:1) to afford 5.35 g of the title compound as a colorless solid of m.p. 232°C. MS: 234.2 (MH^+). TLC: Rf = 0.30 (toluene/ethyl acetate 20:1).

G2. 2-Amino-5-(4-dimethylamino-phenyl)-3-nitro-pyridine

4.36 g of 2-amino-5-bromo-3-nitropyridine are dissolved in 73 ml of anoxic dioxane under a nitrogen atmosphere. Subsequently, 60 ml of an aqueous sodium bicarbonate solution (2.0 M), 7.3 g of 4-dimethylaminophenyl-boronic acid, and 0.886 g of *trans*-dichloro-bis(tricyclohexylphosphane)palladium-(II) are added. The reaction mixture is refluxed at 110°C for 19 hours. Thereafter, the volatile components are removed in vacuo and the remaining residue is redissolved in 1.0 l of a mixture of water/dichloromethane (1:1). The aqueous phase is extracted four times each with 500 ml of dichloromethane. The organic layer is separated, dried using sodium sulfate, and evaporated to dryness to yield a colorless, crude solid. Subsequently, the residue is purified by flash chromatography on silica gel (eluent: dichloromethane/ethanol 50:1) to afford 3.41 g of the title compound as a colorless solid of m.p. 212°C. MS: 259.2 (MH^+). TLC: Rf = 0.55 (dichloromethane/ethanol 50:1).

G3. 2-Amino-5-(4-p-tolyl)-3-nitro-pyridine

Compound G3 can be prepared analogously as described in Example G1 and G2.

Commercial applicability

The compounds according to the invention have valuable pharmacological properties which make them commercially utilizable. They are selective inhibitors of the enzyme inducible nitric oxide synthase. Nitric oxide synthases (NO-syntases, NOSs) are enzymes that generate NO and citrulline from the amino acid arginine. In certain pathophysiological situations such as arginine depletion or tetrahydrobiopterin depletion the generation of O_2^- from NO-synthases instead or together with NO has been reported. NO is long known as a signalling molecule in most living organisms including mammals and humans. The most prominent action of NO is it's smooth muscle relaxing activity, which is caused on the molecular level by the activation of soluble guanylate cyclase. In the last years a lot of other enzymes have been shown to be regulated by NO or reaction products of NO.

There exist three isoforms of NO-synthases which fall into two classes and differ in their physiologic functions and molecular properties. The first class, known as constitutive NO-synthases, comprises of the endothelial NO-synthase and the neuronal NO-synthase. Both isoenzymes are expressed constitutively in various cell types, but are most prominent in endothelial cells of blood vessel walls (therefore called endothelial NO-synthase, eNOS or NOS-III) and in neuronal cells (therefore called neuronal NO-synthase, nNOS or NOS-I). Activation of these two enzymes is dependent on Ca^{2+}/Calmodulin which is generated by transient increases of the intracellular free Ca^{2+} concentration. Activation of constitutive isoforms leads to transient bursts of nitric oxide resulting in nanomolar cellular or tissue NO concentrations. The endothelial isoform is involved in the physiologic regulation of blood pressure. NO generated by the neuronal isoform seems to have neurotransmitter function and the neuronal isoform is among other regulatory processes involved in memory function (long term potentiation).

In contrast to the constitutive isoforms the activation of inducible NO-synthase (iNOS, NOS-II), the sole member of the second class, is performed by transcriptional activation of the iNOS-promoter. Proinflammatory stimuli lead to transcription of the gene for inducible NO-synthase, which is catalytically active without increases in the intracellular Ca^{2+}-concentration. Due to the long half live of the inducible NO-synthase and the unregulated activity of the enzyme, high micromolar concentrations of NO are generated over longer time periods. These high NO-concentrations alone or in cooperation with other reactive radicals such as O_2^- are cytotoxic. Therefore, in situations of microbial infections, iNOS is involved in cell killing by macrophages and other immune cells during early nonspecific immune responses.

There are a number of pathophysiological situations which among others are characterized by the high expression of inducible NO-synthase and concomitant high NO or O_2^- concentrations. It has been shown that these high NO concentrations alone or in combination with other radical species lead to tissue and organ damage and are causally involved in these pathophysiologies. As inflammation is characterized by the expression of proinflammatory enzymes, including inducible NO-synthase, acute and chronical inflammatory processes are promising diseases for the therapeutic application of

selective inhibitors of inducible NO-synthase. Other pathophysiologies with high NO-production from inducible NO-synthase are several forms of shock (septic, hemorrhagic and cytokine-induced).
It is clear that nonselective NO-synthase inhibitors will lead to cardiovascular and neuronal side effects due to concomitant inhibition of constitutive NO-synthase isoforms.

It has been shown in in-vivo animal models of septic shock that reduction of circulating plasma NO-levels by NO-scavenger or inhibition of inducible NO-synthase restores systemic blood pressure, reduces organ damage and increases survival (deAngelo Exp. Opin. Pharmacother. 19-29, 1999; Redl et al. Shock 8, Suppl. 51, 1997; Strand et al. Crit.Care Med. 26, 1490-1499, 1998). It has also been shown that increased NO production during septic shock contributes to cardiac depression and myocardial dysfunction (Sun et al. J. Mol.Cell Cardiol. 30, 989-997, 1998). Furthermore there are also reports showing reduced infarct size after occlusion of the left anterior coronary artery in the presence of NO-synthase inhibitors (Wang et al. Am. J. Hyperttens. 12, 174-182, 1999). Considerable inducible NO-synthase activity is found in human cardiomyopathy and myocarditis, supporting the hypothesis that NO accounts at least in part for the dilatation and impaired contractility in these pathophysiologies (de Belder et al. Br. Heart. J. 4, 426-430, 1995).

In animal models of acute or chronic inflammation, blockade of inducible NO-synthase by isoform-selective or nonselective inhibitors or genetic knock out improves therapeutic outcome. It is reported that experimental arthritis (Connor et al. Eur. J. Pharmacol. 273, 15-24, 1995) and osteoarthritis (Pelletier et al. Arthritis & Rheum. 41, 1275-1286, 1998), experimental inflammations of the gastro-intestinal tract (Zingarelli et al. Gut 45, 199-209, 1999), experimental glomerulonephritis (Narita et al. Lab. Invest. 72, 17-24, 1995), experimental diabetes (Corbett et al. PNAS 90, 8992-8995, 1993), LPS-induced experimental lung injury is reduced by inhibition of inducible NO-synthase or in iNOS-knock out mice (Kristof et al. Am. J. Crit. Care. Med. 158, 1883-1889, 1998). A pathophysiological role of inducible NO-synthase derived NO or O_2^- is also discussed in chronic inflammatory diseases such as asthma, bronchitis and COPD.

Furthermore, in models of neurodegenerative diseases of the CNS such as MPTP-induced parkinsonism, amyloid peptide induced Alzheimer's disease (Ishii et al., FASEB J. 14, 1485-1489, 2000), malonate induced Huntington's disease (Connop et al. Neuropharmacol. 35, 459-465, 1996), experimental menengitis (Korytko & Boje Neuropharmacol. 35, 231-237, 1996) and experimental encephalitis (Parkinson et al. J. Mol. Med. 75, 174-186, 1997) a causal participation of NO and inducible NO-synthase has been shown.

Increased iNOS expression has been found in the brains of AIDS victims and it is reasonable to assume a role of iNOS in AIDS related dementia (Bagasra et al. J. Neurovirol. 3 153-167, 1997).

Other studies implicated nitric oxide as a potential mediator of microglia dependent primary demyelination, a hallmark of multiple sklerosis (Parkinson et al. J. Mol. Med. 75, 174-186, 1997).

An inflammatory reaction with concomitant expression of inducible NO-synthase also takes place during cerebral ischemia and reperfusion (ladecola et al. Stroke 27, 1373-1380, 1996). Resulting NO together with O_2^- from infiltrating neutrophils is thought to be responsible for cellular and organ damage. Also, in models of traumatic brain injury (Mesenge et al. J. Neurotrauma 13, 209-214, 1996; Wada et al. Neurosurgery 43, 1427-1436, 1998) NO-synthase inhibitors have been show to posses protective properties. A regulatory role for inducible NO-synthase has been reported in various tumor cell lines (Tozer & Everett Clin Oncol. 9. 357-264, 1997).

On account of their inducible NO-synthase-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine and therapeutics, where an excess of NO or O_2^- due to increases in the activity of inducible NO-synthase is involved. They can be used without limitation for the treatment and prophylaxis of the following diseases:

Acute inflammatory diseases: Septic shock, sepsis, SIRS, hemorrhagic shock, shock states induced by cytokine therapy (IL-2, TNF), organ transplantation and transplant rejection, head trauma, acute lung injury, ARDS, inflammatory skin conditions such as sunburn, inflammatory eye conditions such as uveitis, glaucoma and conjunctivitis.

Chronic inflammatory diseases of peripheral organs and the CNS: gastrointestinal inflammatory diseases such as Crohn's disease, inflammatory bowel disease, ulcerative colitis, lung inflammatory diseases such as asthma and COPD, arthritic disorders such as rheumatoid arthritis, osteoarthritis and gouty arthritis, heart disorders such as cardiomyopathy and myocarditis, artherosklerosis, neurogenic inflammation, skin diseases such as psoriasis, dermatitis and eczema, diabetes, glomerulonephritis; dementias such as dementias of the Alzheimer's type, vascular dementia, dementia due to a general medical condition, such as AIDS-, Parkinson's disease, Huntington's induced dementias, ALS, multiple sklerosis; necrotizing vasculitides such as polyarteritis nodosa, serum sickness, Wegener's granulomatosis, Kawasaki's syndrom; headaches such as migraine, chronic tension headaches, cluster and vascular headaches, post-traumatic stress disorders; pain disorders such as neuropathic pain; myocardial and cerebral ischemia/reperfusion injury.

The compounds may also be useful in the treatment of cancers that express nitric oxide synthase.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the abovementioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions having an iNOS inhibitory activity.

The invention furthermore relates to pharmaceutical compositions for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

The pharmaceutical compositions are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries or excipients which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral and intravenous delivery are preferred.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation in the form of an aerosol; the aerosol particles of solid, liquid or mixed composition preferably having a diameter of 0.5 to 10 μm, advantagously of 2 to 6 μm.

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those pharmaceutical compositions which are suitable for topical application. For the production of the pharmaceutical compositions, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The pharmaceutical compositions according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for iNOS inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarily between 0.1 and 10 mg per day. The customary dose in the case of systemic therapy (p.o.) is between 0.3 and 30 mg/kg per day, (i. v.) is between 0.3 and 30 mg/kg/h.

Biological investigations

Measurement of inducible NO-synthase activity

The assay is performed in 96-well microtiter F-plates (Greiner, Frickenhausen, FRG) in a total volume of 100 µl in the presence of 100 nM calmodulin, 226 µM $CaCl_2$, 477 µM $MgCl_2$, 5 µM flavin-adenine-dinucleotide (FAD), 5 µM flavin mononucleotide (FMN), 0.1 mM NADPH, 7 mM glutathione, 10 µM BH4 and 100 mM HEPES pH 7.2. Arginine concentrations are 0.1 µM for enzyme inhibition experiments. 150000 dpm of [^{3}H]arginine are added to the assay mixture. Enzyme reaction is started by the addition of 4 µg of a crude cytosolic fraction containing human inducible NO-synthase and the reaction mixture is incubated for 45 to 60 min at 37°C. Enzyme reaction is stopped by adding 10 µl of 2M MES-buffer pH 5,0. 50 µl of the incubation mixture are transferred into a MADP N65 filtration microtiter plate (Millipore, Eschborn, FRG) containing already 50 µl of AG-50W-X8 cation exchange resin (Biorad, München, FRG). The resin in the Na loaded form is pre-equilibrated in water and 70 µl (corresponding to 50 µl dry beads) are pipetted under heavy stirring with a 8 channel pipette into the filtration plate. After pipetting 50 µl of the enzyme reaction mixture onto the filtration plates, the plates are placed on a filtration manifold (Porvair, Shepperton, UK) and the flow through is collected in Pico scintillation plates (Packard, Meriden, CT). The resin in the filtration plates is washed with 75 µl of water (1x50 µl and 1x 25 µl) which is also collected in the same plate as the sample. The total flow through of 125 µl is mixed with 175 µl of Microscint-40 scintillation cocktail (Packard) and the scintillation plate is sealed with TopSeal P-foil (Packard). Scintillation plates are counted in a szintillation counter.

For the measurement of inducible NO-synthase-inhibiting potencies of compounds increasing concentrations of inhibitors were included into the incubation mixture. IC_{50}-values were calculated from the percent inhibition at given concentrations by nonlinear least square fitting.

The inhibitory values determined for the compounds according to the invention follow from the following table A, in which the compound numbers correspond to the example numbers.

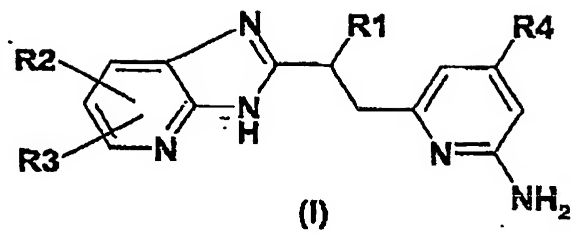
Table A

Inhibition of iNOS activity [measured as -logIC$_{50}$ (mol/l)]

compound	-logIC$_{50}$
1	The inhibitory values of these mentioned Examples lie in the range from 7.18 to 8.15
2	
4	
5	
6	
7	
8	
9	
10	
11	
12	

Patent claims

1. Compounds of formula I



(I)

in which

R1 is hydrogen or 1-4C-alkyl,

R2 is hydrogen, halogen, hydroxyl, nitro, amino, 1-7C-alkyl, trifluoromethyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono- or di-1-4C-alkylaminosulfonyl, 1-4C-alkylcarbonylamino, 1-4C-alkylsulfonylamino, phenyl, R21- and/or R211-substituted phenyl, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl wherein the phenyl moiety is substituted by R22, phenyl-1-4C-alkoxy, pyridyl, pyridyl substituted by R23, pyridyl-1-4C-alkyl, pyridyl-1-4C-alkyl wherein the pyridyl moiety is substituted by R24, in which

R21 is cyano, halogen, carboxyl, 1-4C-alkyl, 1-4C-alkoxy, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonyl, aminosulfonyl, mono- or di-1-4C-alkylaminosulfonyl, amino, mono- or di-1-4C-alkylamino, trifluoromethyl, hydroxyl, phenylsulfonylamino or phenyl-1-4C-alkoxy,

R211 is halogen or 1-4C-alkoxy,

R22 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R23 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R24 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R4 is 1-4C-alkyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

2. Compounds of formula I as claimed in claim 1 in which

R1 is hydrogen or 1-2C-alkyl,

R2 is hydrogen, halogen, phenyl, or R21-substituted phenyl, in which

R21 is 1-4C-alkyl, cyano, halogen, mono- or di-1-4C-alkylamino or trifluoromethyl,

R3 is hydrogen,

R4 is methyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

3. Compounds of formula I as claimed in claim 1 in which

R1 is hydrogen, methyl or ethyl,

R2 is hydrogen, iodine, bromine, phenyl, or R21-substituted phenyl, in which

R21 is methyl, cyano, chlorine, fluorine, dimethylamino or trifluoromethyl,

R3 is hydrogen,

R4 is methyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

4. Compounds of formula I according to claim 1 in which R4 is methyl, and the salts, the N-oxides and the salts of the N-oxides of these compounds.

5. Compounds of formula I according to any of the proceding claims in which R4 is methyl and R1 is hydrogen, and the salts, the N-oxides and the salts of the N-oxides of these compounds.

6. Compounds of formula I according to claim 1 for use in therapy, e.g. for the treatment of diseases.

7. Pharmaceutical compositions containing one or more compounds of formula I according to claim 1 together with the usual pharmaceutical auxiliaries and/or excipients.

8. Use of compounds of formula I according to claim 1 for the production of pharmaceutical compositions for the treatment of acute inflammatory diseases.

9. Use of compounds of formula I according to claim 1 for the production of pharmaceutical compositions for the treatment of chronic inflammatory diseases of peripheral organs and the CNS.

10. A method for treating acute inflammatory diseases in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula I according to claim 1.

11. A method for treating chronic inflammatory diseases of peripheral organs and the CNS in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula I according to claim 1.

Abstract

The compounds of formula I in which R1, R2, R3 and R4 the meanings as given in the description ar
novel effective iNOS inhibitors.

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